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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,254	09/14/2000	Richard W. Moyer	UF-221C1XC1	2442

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	25

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/662,254	Moyer
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Nov 15, 2002* .

2a) X This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *76-90 and 92-102* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) X Claim(s) *101 and 102* is/are allowed.

6) X Claim(s) *76-90, 92, 95, 97, 99, and 100* is/are rejected.

7) X Claim(s) *93, 94, 96, and 98* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). *24*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendments received 11/15/02 (c.m. 8/26/02) has been entered. Claims 76-90 and 92-102 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Double Patenting

The rejection of claims 76-78, 81, and 83-89 for obviousness-type double patenting over U.S. Patent No. 6,106,825 is withdrawn in view of applicant's submission of a terminal disclaimer.

Claim Rejections - 35 USC § 112

The rejection of claims 76-89 under 35 U.S.C. 112, first paragraph, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action stated that while the specification provides an enabling disclosure for the **non-therapeutic** delivery of polynucleotides encoding a protein to vertebrate

cells *in vivo* using the disclosed rEPV wherein the polynucleotide encoding the protein is operably linked to an **early pox virus** promoter, the specification fails to provide sufficient enablement for the use of a non-pox virus promoter to express proteins of interest *in vivo*. Previous office action have further indicated that the specification is also enabling for the delivery of polynucleotides encoding a protein to vertebrate cells ***in vitro*** using the disclosed rEPV wherein the polynucleotide encoding the protein is operably linked to an early pox virus promoter or non-pox virus promoter.

The previous office actions stated that page 75 of the instant specification teaches how to construct an rEPV comprising CMV and TK promoters operably linked to marker genes. Page 85 of the specification teaches that the rEPV disclosed on page 75 can infect cells *in vitro* and that after multiple rounds of selection, cells expressing both marker genes can be detected. Expression from non-poxvirus promoters requires the participation of cell based factors rather than entomopox factors, as such, both the specification and the art teach that expression using promoters such as CMV or HSV-TK requires the integration of the recombinant EPV DNA into the host cell's genome such that it is accessible to host transcription factors. The applicant's data clearly demonstrates that integration following infection with rEPV is not a high percentage event such that detection of cells which may express the recombinant protein of interest requires several rounds of selection to increase the number of cells with the integrated DNA. The specification fails to provide sufficient guidance as to dosages or routes of administration of rEPV which utilize non-pox virus promoters to vertebrates such that rEPV DNA integrates into the host's cells *in*

vivo and results in detectable amounts of protein expression. Further, the specification does not provide any guidance as to methods of selecting for cells with integrated EPV DNA *in vivo* such that the expression of the heterologous gene can be detected *in vivo*. Thus, based on the mechanism of expression of a heterologous gene from an rEPV using a non-pox virus promoter, the lack of guidance provided by the specification for dosages, routes of delivery, and selection methods for expressing detectable amounts of protein in vivo by administering rEPV encoding a heterologous protein under transcriptional control of any non-pox virus promoter, and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed.

The applicant argues that they are not claiming expression *in vivo* at a particular level of efficiency, or a particular level of expression. However, the applicant is reminded that the claims have been evaluated based on the specification's teachings of how to use the instant methods. As noted in previous office actions, the specification teaches that the instant methods are to be used to the expression of a detectable marker gene, or the expression of therapeutic levels of a protein. Thus, the level of vector transduction, integration, and expression of the heterologous gene *in vivo* are relevant to the use of the these vectors as taught in the specification. The specification does not provide any use for the instant methods wherein the heterologous gene is delivered but not expressed at detectable levels.

The applicant further argues that *in vitro* expression assays are recognized as a reasonable predictor of achieving detectable expression *in vivo*, and that despite applicant's use of multiple

rounds of selection *in vitro*, selection is not required to practice applicant's invention *in vivo*. Applicant's arguments have not been found persuasive in regards to the use of a non-pox virus promoter to express proteins of interest *in vivo*. As noted above, the *in vitro* data in the specification demonstrates that several rounds of selection were required before expression of the marker protein could be detected. Applicant's statement that multiple rounds of selection merely provides a reliable count of transduced cells over time is not an accurate portrayal of the G418 selection method. G418 selection of cells is a positive selection event, meaning that only cells which have been infected with the rEPV and which express NeoR at a level sufficient to protect cells against G418 will survive and divide in the presence of G418. The fact that several rounds of positive selection were required in order to detect marker gene expression indicates that the percentage of cells infected with the rEPV was extremely low and/or the level of expression of the marker protein by rEPV was extremely low. This is in contrast to transduction of cells with AAV as exemplified by U.S. Patent 5,962,313, cited by the applicants are proof that *in vitro* transduction with an integrating virus correlates with *in vivo* transduction and expression. U.S. Patent 5,962,313 demonstrates 30% transduction efficiency *in vitro* of their target cell and substantial expression **without** any selection of transduced cells (U.S. Patent 5,962,313, column 21, lines 39-54). Thus, applicant's arguments regarding U.S. Patent 5,962,313 are not persuasive, as the AAV vector is capable of substantial transduction and expression without selection. As such, a nexus between the successful use of the AAV vector, a vector with natural tropism for vertebrate cells, and the applicant's rEPV cannot be found. Furthermore, as discussed

in previous office actions, the applicants have not disclosed or exemplified *in vivo* selection of rEPV transduced cells *in vivo*. The applicant is reminded that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. Thus, based on the mechanism of expression of a heterologous gene from an rEPV using a non-pox virus promoter, the lack of guidance provided by the specification for dosages, routes of delivery, and selection methods for expressing detectable amounts of protein *in vivo* by administering rEPV encoding a heterologous protein under transcriptional control of any non-pox virus promoter, and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed.

Claim Rejections - 35 USC § 102

The rejection of claims 90, 92, 95, 97, and 99-102 under 35 U.S.C. 102(e) as being anticipated by Dall et al. is **withdrawn** over claims 101-102 in view of applicant's amendment to claim 101, and **maintained** over claims 90, 92, 95 and 97. Applicant's amendment to claim 90 and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the amendment to claim 90 which adds the limitation that the non-poxvirus promoter is activated by the cellular RNA polymerase of a vertebrate cell is

unpersuasive in view of the teachings of Dall et al. Dall et al. teaches entomopoxvirus vectors and viruses comprising a heterologous DNA selected from a group including interferons, and human growth hormone (Dall et al., column 21-22, claims 1-28) Dall et al. further teaches that the heterologous DNA is expressed using the heterologous gene's natural promoter (Dall et al., column 3, lines 30-39). As the natural promoter of the heterologous human growth hormone gene taught by Dall et al. is naturally active in human cells which utilize human RNA polymerase for transcription, Dall et al. teaches all the elements of the claims as written.

The MPEP states that, "Where the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. MPEP 211.01 and In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 93-94, 96, and 98 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 101-102 are considered free of the prior art of record and allowable at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's

supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER